REMARKS

Claims 31-50 are pending in the case. Claim 31 has been deemed allowable.

Applicant notes that the Office Action mentions claims 31-50 as pending in this case based on a change in claim numbering. The present response reflects the new claim numbers and the claim dependencies have been changed to reflect this new numbering.

Rejection Under 35 U.S.C. §102

Claims 32-40, 42-46 and 48 were rejected under section 102(b) as anticipated by Lizardi et al (Nature Genetics, 1998).

Here, the rejection relies on Lizardi's teaching regarding the RCA-CACHET method (as in Figure 6 of Lizardi). However, the method disclosed in Lizardi et al (described in the legend of Figure 6 as the "RCA-CACHET ligation dependent assay" and specifically shown in step 3 of the process disclosed in this figure) relies on ligation to determine whether amplification occurs or not and the Examiner notes later in the Office Action (in "Response to Arguments") that the claims do not recite that a ligation step is not encompassed because of the use of "comprising" language in the claim. In response, Applicants have included in claim 32, and thus all of the claims dependent therefrom, i.e., claims 33-50, that a ligase-dependent step is not employed. Because the method of amended claim 32 and claims dependent therefrom, excludes use of a ligation step (supported throughout the application, for example, at page 12, lines 8-9, describing the embodiment of Figure 1), they cannot be either anticipated or rendered obvious by an art reference that relies on such a procedure. Lizardi teaches nothing that does not require

ligation.

Rejection Under 35 U.S.C. §103(a)

Claims 32, 34-40 and 42-48 were rejected as obvious over Valimaa et al (1998) in view of Chee et al (U.S. Patent 6,355,431).

Applicant responds that claim 32, as amended, and those claims dependent from it, either directly or indirectly, are not rendered obvious by these references, either alone or in combination.

Valimaa et al relies on use of the polymerase chain reaction (PCR) to amplify a specific allele (not necessarily an SNP) while Chee et al teaches the desirability of RCA as a means of amplification. However, to combine these references, one must combine the RCA of Chee et al with the PCR method of Valimaa et al. This cannot be done.

Chee teaches only RCA that involves a ligation step (described as a ligation dependent procedure by Chee et al at column 19, lines 20, 33 and 54, thereof). Conversely, the PCR procedure of Valimaa et al does not provide for a ligation step that would serve as an amplification target circle, essential to Chee et al. Thus, Valimaa et al teaches only use of PCR to determine alleles (not SNPs, which are not mentioned therein) while Chee et al suggests that ligation-dependent RCA is useful for amplification procedures. Combination of these two references, even if possible, is irrelevant to Applicant's claim 32, as amended, because no ligation step is encompassed thereby.

In addition, as Applicant has noted in a prior amendment, Chee uses RCA to amplify a sequence only after single base extension while in Valimaa the extended sequences have already been amplified by PCR.

In view of the amendment to claim 32, Applicant respectfully urges that this ground of rejection be withdrawn.

Claims 32-40, 42-46 and 48-50 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi et al (Nature Genetics, 1998) in view of Ishikawa et al (Human Immunology, 1995).

In response, Applicant notes that the rejection relies, in part, on Lizardi's teaching of Figure 2 (which describes "Ligation of circularizable probes", and at page 231, describing "Probe Ligations using gap oligonucleotides or gap-filing." Such "gap oligonucleotides" must be inserted with a ligase enzyme. Applicant reiterates the above-arguments regarding amended claim 2, wherein a ligation step is excluded from coverage. Without ligation, none of these methods work and Lizardi teaches at most the use of ligation reactions to detect SNPs.

Thus, Lizardi is not relevant to amended claim 1 with or without combination with Ishikawa et al, which only teaches a mismatch at the second position from the 3'-end (not positions 1 and/or 3 as in amended claim 32) to improve annealing during thermocycling (see page 316, column 2, paragraph beginning "Figure 2 shows..." and also see the description of Figure 2 on page 317 of Ishikawa) and not in detection of any nucleotide mismatches (i.e., it is a very different technological problem being solved by Ishikawa et al versus either Lizardi et al or the method of claim 32).

Claims 32, 34-40 and 42-50 were rejected as obvious over Valimaa et al (1998) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Ishikawa et al (Human Immunology, 1995).

Here, the Examiner attempts to combine these 3 references by relying on the

arguments for Valimaa et al and for Chee et al in combination with Ishikawa et al, stating that "Ishikawa teaches that putting mismatches in primers near the 3'-termini increases the specificity of amplification."

In response, Applicant again notes that amended claim 32 does not encompass any ligation step whereas the RCA methods recited in Chee et al rely on such a step. In addition, regardless of whether Ishikawa et al teaches the use of mismatches to increase specificity of amplification, this reference does not teach that inserting mismatches increases allele discrimination as recited in Applicant's claim 32 because here the mismatch is for the purpose of increasing specificity of the SNP detection (step (b) of the claim) whereas the amplification step (step (c) of the claim) does not depend on any mismatches. It is the amplification target circle that is being amplified (using P2) and not the mismatched probe (P1). Thus, in claim 32, the mismatch and the amplification occur at different stages of the recited method. Because Applicant's amplification step involves no mismatches, one would not combine the references with Ishikawa to achieve the method of claim 32, even without the amendment regarding absence of a ligation step (on which the Chee et al RCA procedure depends – see above).

Claims 32-40 and 42-50 were rejected as obvious over Valimaa et al (1998) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Lizardi et al (Nature Genetics, 1995).

In response, Applicant reiterates that Valimaa et al (1998) and Chee et al (U.S. Patent 6,355,431) do not teach the limitations of claim 32 (or any of the claims dependent therefrom) for the reasons already stated. In sum, Chee teaches only ligation dependent RCA whereas amended claim 32 teaches use of methods that do not involve ligation, while Valimaa teaches use of PCR and not RCA. Thus, whether or not Lizardi teaches use of bipolar primers is not relevant. These references cannot produce the method of amended claim 32, regardless of how they are combined.

Applicant also notes that the 3'-5'-3' (bipolar) primer of Lizardi et al is ligated to the P1 primer and the resulting oligonucleotide is amplified by RCA. Such a bipolar primer could not be used at all in the method of Chee because in Chee the ATC is formed by ligation of the primer ends, or by ligation of adjacent primers (in both cases, ligation requires adjacent 5' and 3' ends), so that a bipolar primer (with two 3' ends) is unnecessary and one would therefore not be motivated to use it. Thus, Lizardi could not be combined with Chee regardless of what Valimaa teaches.

Claims 32-40 and 42-48 were rejected as obvious over Lizardi et al (Nature Genetics, 1995) in view of Chee et al (U.S. Patent 6,355,431) on grounds that Lizardi et al teach the limitations of claim 32 while Chee et al teach the use of target sequences i Cancer.

In response, Applicant reiterates that Lizardi et al does not teach the limitations of amended claim 32 (but only ligation-dependent methods, be they enzymatic or chemically catalyzed) and Chee's teaching of uses of target sequences in detecting cancer does not help Lizardi achieve the method of Applicant's claim 32, or any of the claims dependent therefrom.

Furthermore, in Lizardi the adjacent primers form on the target sequence, are then ligated, the target removed and the ATC is bound to the ligated oligonucleotide. This cannot work in Chee, which uses the adjacent primers to form the ATC whereas Lizardi uses them to bind the ATC and so, again, one is not motivated to look to, much less to combine, these references. Lizardi simply does not teach use of such a primer in the way that it would be used by Applicant in the claimed invention (as in claim 33), or in Chee, where the ATC is formed by ligation of the primers.

In view of the amendments made herein, as well as the foregoing arguments,

Applicants believe that the cited grounds of rejection have been overcome and that the claims are in condition for allowance.

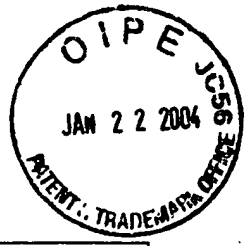
Applicant acknowledges the allowance of claim 31 but has made some minor amendments thereto that are believed to increase the clarity of the claim.

Applicant also notes the suggested claim interpretation applied by the Examiner to claim 31. The claim is recited as it is because, from review of the embodiments of Figures 1 and 2, the detection of an SNP could work by using a probe that matches the wild type target sequence so that amplification indicates no mutation, or the probe could contain the mutant form (see, for example, claim 42) so that a mutant target would match the probe and afford subsequent amplification. Thus, the probe contains terminal and 3rd from terminal nucleotides that may or may not be complementary so as to afford freedom in how to conduct the test.

In addition, regarding claim 41, which recites a number of specific nucleotide sequences for use as probes in the method of claim 32, Applicant urges that if the generic matter of claim 32 is deemed allowable, then the limitations of claim 41 should also be allowable without regard to which specific sequences are employed as probes and thus claim 41 should be allowed as well.

The present response includes a Request for a 1 month extension of time to respond, under 37 C.F.R. 1.136(a) and a check to cover the cost for a small entity. The Commissioner is authorized to charge payment of any additional filing fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

Serial No.: 09/827,289
Filed: 5 April 2001



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